PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 31144	FOR FURTHER ACTION	See Form PCT/IPEA/416
International application No. PCT/IL06/00059	International filing date *(day/month/year)* 15 January 2006 (15.01.2006)	Priority date *(day/month/year)* 13 January 2005 (13.01.2005)
International Patent Classification (IPC) or national classification and IPC IPC: **G01T 1/166**(2006.01);**A61B 5/05**(2006.01),**6/00**(2006.01);**G06K 9/00**(2006.01) USPC: 250/370.08,363.04		
Applicant SPECTRUM DYNAMICS LLC		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 4 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *(sent to the applicant and to the International Bureau)* a total of 8 sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) _____ , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).
4. This report contains indications relating to the following items:
   - ☒ Box No. I Basis of the report
   - ☐ Box No. II Priority
   - ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - ☒ Box No. IV Lack of unity of invention
   - ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - ☐ Box No. VI Certain documents cited
   - ☐ Box No. VII Certain defects in the international application
   - ☐ Box No. VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
10 January 2007 (10.01.2007)	01 May 2007 (01.05.2007)
Name and mailing address of the IPEA/ US Mail Stop PCT, Attn: IPEA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (571) 273-3201	Authorized officer Rhonda for Bell Constantine Hannaher Telephone No. (571) 272-2437

Form PCT/IPEA/409 (cover sheet)(April 2005)

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/IL06/00059

Box No. I Basis of the report

1. With regard to the **language**, this report is based on:

☒ the international application in the language in which it was filed.

☐ a translation of the international application into English, which is the language of a translation furnished for the purposes of:

☐ international search (under Rules 12.3 and 23.1(b))

☐ publication of the international application (under Rule 12.4(a))

☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

☐ the international application as originally filed/furnished

☒ the description:
pages 1,3-7,9-13,16-101 and 103 as originally filed/furnished
pages* 2,8,14,15 and 102 received by this Authority on 10 January 2007 (10.01.2007)
pages* NONE received by this Authority on

☒ the claims:
pages 107 as originally filed/furnished
pages* NONE as amended (together with any statement) under Article 19
pages* 104-106 received by this Authority on 10 January 2007 (10.01.2007)
pages* NONE received by this Authority on

☒ the drawings:
pages 1/94-94/94 as originally filed/furnished
pages* NONE received by this Authority on
pages* NONE received by this Authority on

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages
☐ the claims, Nos.
☐ the drawings, sheets/figs
☐ the sequence listing (*specify*):
☐ any table(s) related to the sequence listing (*specify*):

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

☐ the description, pages
☐ the claims, Nos.
☐ the drawings, sheets/figs
☐ the sequence listing (*specify*):
☐ any table(s) related to the sequence listing (*specify*):

** If item 4 applies, some or all of those sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/IL06/00059

Box No. IV Lack of unity of invention

1. ☐ In response to the invitation to restrict or pay additional fees the applicant has, within the applicable time limit:

   ☐ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest, and, where applicable, the protest fee

   ☐ paid additional fees under protest but the applicable protest fee was not paid

   ☐ neither restricted the claims nor paid additional fees

2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is:

   ☐ complied with.

   ☒ not complied with for the following reasons:

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

Group I, claim(s) 1, drawn to a method of image reconstruction of a multi-isotope source.

Group II, claim(s) 2-4, drawn to a method of determining a future administration dose.

Group III, claim(s) 5-17, drawn to methods, apparatus, and electronic storage mediums of diagnosing a patient condition.

The inventions listed as Groups I, II, III do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the modeling and solution of Group I is not the same, not does it correspond to, the administration of a reduced, and prediction of a future, radiopharmaceutical dose of Group II, or the measurement by SPECT of a behavior of a radiopharmaceutical in vivo of Group III. Likewise, the special technical features of Group II are not the same as, nor do they correspond to, the special technical features of Group III.

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☒ all parts

   ☐ the parts relating to claims Nos. ____

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/IL06/00059

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims 1-17	YES
	Claims NONE	NO
Inventive Step (IS)	Claims 1-17	YES
	Claims NONE	NO
Industrial Applicability (IA)	Claims 1-17	YES
	Claims NONE	NO

2. Citations and Explanations (Rule 70.7)

Claims 1-17 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest the method of image reconstruction of a multi-isotope source of claim 1, the method for treatment of the human body by therapy of claim 2, the diagnostic methods of claims 5 and 6, or the electronic storage mediums and apparatus for automatic diagnosis of claims 10, 11, and 15.

Claims 1-17 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.

---------- NEW CITATIONS ----------

annihilation takes place. As such, PET imaging collects emission events, which occurred in an imaginary tubular section enclosed by the PET detectors. A gold standard for PET imaging is PET NH_3 rest myocardial perfusion imaging with N-13-ammonia (NH_3), at a dose level of 740 MBq, with attenuation correction [XXX correct}. Yet, since the annihilation gamma is of 0.511 Mev, regardless of the radio-isotope, PET imaging does not provide spectral information, and does not differentiate between radio-isotopes.

In SPECT imaging, primarily gamma emitting radio-isotopes are used for labeling, and the imaging camera is designed to detect the actual gamma emission, generally, in an energy range of approximately 11- 511 KeV. Generally, each detecting unit, which represents a single image pixel, has a collimator that defines the solid angle from which radioactive emission events may be detected.

Because PET imaging collects emission events, in the imaginary tubular section enclosed by the PET detectors, while SPECT imaging is limited to the solid collection angles defined by the collimators, generally, PET imaging has a higher sensitivity and spatial resolution than does SPECT. Therefore, the gold standard for spatial and time resolutions in nuclear imaging is defined for PET.

The radiopharmaceutical behavior in vivo is a dynamic process. Some tissues absorb radiopharmaceuticals faster than others or preferentially to others, and some tissues flush out the radiopharmaceuticals faster than others or preferentially to others, so the relative darkness of a given tissue is related to a time factor. Since the uptake clearance of such a radiopharmaceutical by the various tissues (target and background) varies over time, standard diagnosis protocols usually recommend taking an image at the time at which the ratio of target emission versus background emission is the highest.

Yet, this approach produces a single parameter per voxel of the reconstructed image, a level of gray, at a specific time, and ignores the information that could be obtained from the behavior of a radiopharmaceutical as a function of time.

Dynamic imaging, on the other hand, attempts to acquire the behavior of a radiopharmaceutical as a function of time, for example, to measure perfusion in myocardial tissue. Dynamic imaging is advantageous to static imaging, as it provides a better measure of blood flow, it is more sensitive to ischemia than static imaging,

iii. applying algorithm which select a preferred set of views to for ROI focusing, based on the geometry of the organ to be imaged;

iv. zooming in, by a second algorithm tic iteration, to select a preferred set of views based on earlier findings;

v. active vision, which ensures that each detector obtains the maximum information from any position;

6. calibration sources, which may be placed on the body, within a body lumen, or near the camera;

11. the use of the calibration sources of (6) to obtain an attenuation map;

12. ultrasound-based, or MRI based attenuation correction (our 26137);

13. ultrasound-based attenuation correction using ultrasound patches, such as patch-sensor devices, described in U.S. Patents 5,807,268; 5,913,829 and 5,885,222, all of which are assigned to MedAcoustics, Inc., Raleigh, NC, USA, both for structural mapping, for correlating the structural map with the functional map, and for attenuation correction. The ultrasound patches may be incorporatred with the radiopharmaceutical calibration sources;

14. minimal multiplexing between the detectors and the analyzer, to prevent saturation;

15. customizing to the patient imaging parameters such as overall camera configuration, angular travel of each sweep, sweeping speed, translational travel, angular and (or) translational steps, total imaging time, and the like.

The camera sensitivity may be determined by at least one of the following:

1. a sensitivity in terms of speed of data collection and spatial resolution, at least as good as a gold standard for PET imaging for at rest myocardial perfusion with N-13-ammonia (NH_3);

2. a sensitivity sufficient for reconstructing an image under a Cobalt wire Nema test of a line source of 5 mCi cobalt with a line spread function of less than 7 mm Full Width Half Maximum (FWHM) through air at a distance of at least 100 mm;

3. a sensitivity sufficient for resolving through air at a distance of at least 100 mm under a Nema Bar Phantom test of gaps formed between 1 mm wide led bars positioned less than 7 mm apart from one another over a uniform cobalt disc;

account toxicity, radiation dose, clearance rate, uptake rate by an organ, or any other measurements, as provided by the first administration, to weigh benefit and potential harm.

The effects, which were combined to increase the camera's sensitivity and resolutions, are as follows:

1. solid collection angles greater than 0.1 or 0.15 steradians;
2. close proximity of the detectors to the body, in order to increase both:
   i. detection efficiency, which falls as a proportionally to the square of the distance from an object; and
   ii. resolution, where the number of detector pixels which view an object also falls proportionally to the square of the distance from the object;
3. windshield-wiper sweeping motions, with a center of rotation outside the patient's body, to maximize the information obtained from each x;y;z detector position;
4. trio-vision of each voxel, wherein each voxel is viewed with x, y, and z, components, as opposed to stereo vision in a plane, with only x and y components of state-of-the-art cameras;
5. Focus on a region of interest, by:
   i. prescanning;
   ii. independent motion of detectors, for independent focusing on ROI, by each detector;
   iii. applying algorithm which select a preferred set of views to for ROI focusing, based on the geometry of the organ to be imaged;
   iv. zooming in, by a second algorithm tic iteration, to select a preferred set of views based on earlier findings;
   v. active vision, which ensures that each detector obtains the maximum information from any position;
6. calibration sources, which may be placed on the body, within a body lumen, or near the camera;
11. the use of the calibration sources of (6) to obtain an attenuation map;
12. ultrasound-based, or MRI based attenuation correction (our 26137);

13. ultrasound-based attenuation correction using ultrasound patches, such as patch-sensor devices, described in U.S. Patents 5,807,268; 5,913,829 and 5,885,222, all of which are assigned to MedAcoustics, Inc., Raleigh, NC, USA, both for structural mapping, for correlating the structural map with the functional map, and for attenuation correction. The ultrasound patches may be incorporatred with the radiopharmaceutical calibration sources;

14. minimal multiplexing between the detectors and the analyzer, to prevent saturation;

15. customizing to the patient imaging parameters such as overall camera configuration, angular travel of each sweep, sweeping speed, translational travel, angular and (or) translational steps, total imaging time, and the like.

The camera sensitivity may be determined by at least one of the following:

1. a sensitivity in terms of speed of data collection and spatial resolution, at least as good as a gold standard for PET imaging for at rest myocardial perfusion with N-13-ammonia (NH_3);

2. a sensitivity sufficient for reconstructing an image under a Cobalt wire Nema test of a line source of 5 mCi cobalt with a line spread function of less than 7 mm Full Width Half Maximum (FWHM) through air at a distance of at least 100 mm;

3. a sensitivity sufficient for resolving through air at a distance of at least 100 mm under a Nema Bar Phantom test of gaps formed between 1 mm wide led bars positioned less than 7 mm apart from one another over a uniform cobalt disc;

4. a sensitivity operative for image acquisition of a full organ in less than 10 seconds at a spatial resolution, capable of identifying objects not greater than about 7 mm X 7 mm X 7 mm with a signal-to-noise ratio of at least 4 to 1 or better;

5. a sensitivity for detecting at least 1 out of every 5000 emitted photons while allowing a reconstructions of a 3D image with a resolution of not more than 5 mm and energy resolution of not more than 15 %; and

6. having a sensitivity to image a volume of about 5cm diameter located about 150 mm from the detectors, with a total sensitivity of about 1 photons detected out of 65 emitted.

17. Use of C-11-Raclopride to target dopamine D2 receptors, for brain imaging of dopamine D2 receptors in schizophrenia, and assessment of dose for neuroleptics.

18. Use of I-123-iodobenzamide (IBZM) to target dopamine D2 receptors, for brain imaging of dopamine D2 receptors in schizophrenia, and assessment of dose for neuroleptics.

19. C-11-carfentanil to target Mu opioid receptors in brain, with the clinical application of imaging drug addiction.

20. Use of C-11-α-methyl-L-tryptophan as a precursor for α-methyl serotonin synthesis and as a substrate for AAAD enzyme, with the clinical application of imaging depression.

21. Use of C-115-Hydroxytryptophan as a precursor for serotonin synthesis with the clinical application of imaging neuroendocrine tumors.

22. Use of F-18-MPPF to bind to 5-HT1A (5-hydroxytryptamine-1A) serotonin receptors, with the clinical application of imaging depression and epilepsy.

23. Use of F-18-Altanserin to bind to 5-HT2A serotonin receptors with the clinical application of imaging depression and epilepsy.

24. Use of C-11-Acetate for the study of tricarboxylic acid cycle activity and oxidative metabolism with the clinical application of studying myocardial oxygen metabolism.

25. Use of C-11-Palmitate as a precursor for fatty acid metabolism with the clinical application of imaging myocardial metabolism.

26. F-18-Fluorodopamine to target presynaptic adrenergic receptors

<u>Protocols for Beta Emitting Radiopharmaceuticals</u>

The following beta emitting radionuclides may be used for diagnostic studies, using a dose of about 1 mCi, using the camera of the present invention: Sm-153 ($T_{1/2}$ 1.95 days), I-131 ($T_{1/2}$ 8.04 days), Cu-67 ($T_{1/2}$ 2.58 days), Lu-177 ($T_{1/2}$ 6.7 days), and Sn-117m ($T_{1/2}$ 13.6 days). These include both long-lived radiopharmaceuticals and radiopharmaceuticals with low abundance gamma.

What is claimed:

1. A method of image reconstruction of a multi-isotope source, comprising:

modeling photon scatter for each isotope j, based on the Compton scatter equation, relating initial and final photon energies to a Compton scatter angle;

employing an iterative process for generating a solution for the image reconstruction, by describing a probability that an emitted photon of an isotope j, from a voxel u, be detected by a detector t, at an energy bin b.

2. A method for determining a future administration dose, comprising:

i. administering a radiopharmaceutical at no more than one fifth of an expected effective dose;

ii. measuring by SPECT the distribution of the radiopharmaceutical in the body; and

iv. determining the preferred administration dose of the radiopharmaceutical agent for at least one future administration.

3. The method of claim 2, wherein the future administration is of a radiopharmaceutical.

4. The method of claim 2, wherein the future administration is of a therapeutic agent.

5. A method of diagnosing a patient condition, comprising:

defining pathological signatures, each characterized by a unique combination of at least two parameters, which relate to behavior of a radiopharmaceutical in vivo;

measuring the at least two parameters, for a patient, by SPECT imaging; and

automatically diagnosing a pathology of the patient, by automatically matching the at least two parameters and the pathological signatures.

6. A method of diagnosing a patient condition, comprising:

defining pathological signatures, each characterized by a unique combination of at least two patient parameters, at least one of which relating to behavior of a radiopharmaceutical in vivo;

measuring the at least two patient parameters, wherein the at least one patient parameter relating to the behavior of the radiopharmaceutical in vivo is measured by SPECT imaging; and

automatically diagnosing a pathology by automatically matching the at least two patient parameters and the pathological signatures.

7. The methods of claims 5 or 6, wherein automatically diagnosing a pathology comprises automatically diagnosing based on a database of values for normal and diseased populations.

8. The methods of claims 5 or 6, wherein measuring includes measuring at least one radiopharmaceutical kinetic parameter of a flow rate across a tissue membrane.

9. The method of any one of claims 5 or 6, and further including automatically determining the degree of the pathology.

10. An electronic storage medium comprising

at least one radiopharmaceutical identity;

SPECT measured values of at least one radiopharmaceutical kinetic parameter of a flow rate across a tissue membrane, for the radiopharmaceutical, and

a set of instructions for associating the at least one radiopharmaceutical kinetic parameter with a disease signature.

11. Apparatus for performing automatic diagnosis, based on SPECT data, comprising a set of instructions for:

defining pathological signatures, each characterized by a unique combination of at least two patient parameters, at least one of which relating to behavior of a radiopharmaceutical in vivo, as measured by SPECT;

measuring the at least two patient parameters, wherein the at least one patient parameter relating to the behavior of the radiopharmaceutical in vivo is measured by SPECT imaging; and

automatically diagnosing a pathology by automatically matching the at least two patient parameters and the pathological signatures.

12. The apparatus of claim 11, wherein automatically diagnosing a pathology comprises automatically diagnosing based on a database of values for normal and diseased populations.

13. The apparatus of claim 11, wherein measuring includes measuring at least one radiopharmaceutical kinetic parameter of a flow rate across a tissue membrane.

14. The apparatus of claim 12, wherein automatically diagnosing includes determining a degree of a pathology.

15. An electronic storage medium comprising a set of instructions for:

defining pathological signatures, each characterized by a unique combination of at least two patient parameters, at least one of which relating to behavior of a radiopharmaceutical in vivo, as measured by SPECT;

measuring the at least two patient parameters, wherein the at least one patient parameter relating to the behavior of the radiopharmaceutical in vivo is measured by SPECT imaging; and

automatically diagnosing a pathology by automatically matching the at least two patient parameters and the pathological signatures.

16. The electronic storage medium of claim 15, wherein automatically diagnosing a pathology comprises automatically diagnosing based on a database of values for normal and diseased populations.